

# Repercussion and Ways to Overwhelm the Drug Failure in Clinical Trials

Kajal Andotra<sup>1</sup>, Raibarinder Singh<sup>2</sup>

University School of Pharmaceutical Sciences, Rayat Bahra University, Sahauran, Mohali, Punjab, India

**Abstract:** Drug development is a very complex process. It is extremely difficult to find best drug which will increase the success rate of drug in market. Drug faces many challenges during its development. It is not necessary that all scientific inventions translate into a better outcome. The success rate of drug is falling day by day. The main reasons behind drug failure are efficacy, safety and commercial concerns of the drug. Lack of commitment by the companies also leads to high failure rate of drug. Drug failure ultimately impacts human life style as well as their emotional health and has financial impact due to arise of AD6R and unaffordable high price of drug in market. Patent life is an important aspect to sustain a viable business. Shareholders always do one's best to extend the time period of patent expiry for their own profit. Pharmaceutical organizations must adopt best ways to overcome the rate of drug failure. 5R framework enhances the success rate of trials by identifying right target, right patient, right safety, right tissue and right commercial potential for the betterment of emerging future of pharmaceutical industry.. Before the initiation of research, it must be important for all pharmaceutical industries to aware about the drug's history either it shows any ADR in past. Recognition of susceptible drug is mandatory for all pharmaceutical companies which will not lead into mishappening in clinical trials. Inventors or shareholders needs to focus on research process in depth rather than their own profit.

**Keywords:** ADR, NME, FDA, CSDD, 5R

## 1. Introduction

A Drug is a component that is utilized in the detection, cure and also provide protection against any diseases after entered into the market. Drug development process is a very complex process that involves preclinical and clinical phases. Drug faces many challenges during their development process.

In drug development process, there are thousands of compounds which undergoes screening. Out of which only one compound gets market approval by regulatory authorities. This process is very long and expensive. **Identification of a blockbuster drug can act like looking for a needle in a haystack.**<sup>[1]</sup> In drug development, not all scientific invention translates into a good outcome which means that it leads to drug failure. It is not a true statement that all licensed drugs are safe and effective. Sometimes ADR appears before and even after getting market approval. The most extensive survey of clinical success rate over drug development industry conveys that the efficiency of production may be even less than previous approximation.<sup>[2]</sup> By improving the design of trial and project management may provide support for lower the no. of trial that may fail at the latest stages.<sup>[3]</sup> In 2014, only 32% of drugs have probability to move further to phase3 trial and only one in 10 drugs get the market approval.<sup>[1]</sup> The success rate of drugs is even lower in case of major diseases like oncology.<sup>[1]</sup> There are number of scientific advances in R&D that would grow the efficiency and success rate of drug development but still there is significant no. of clinical trials that fail to produce new and safe medicines.<sup>[1]</sup> Approximately 70% of phase2 trials are unsuccessful. Recent PAREXEL analysis is done from mid 2012 to 2015 in which 150,000 patients recruited in phase3 trial that ultimately failed.<sup>[4]</sup> With such a massive economic burden, most trials( in phase3, but sometimes earlier) are vulnerable due to lack of fund and donot have any appropriate chance

to induce a positive result. This will lead to ethical problems concerning to patient enrollment.<sup>[6]</sup>

However failures in RCT's may create knowledge and it cannot be neglected and negative trials may assist towards raising costs for drug development process and higher toxicity.<sup>[7]</sup>

The prices of failed clinical trials are increasing day by day but the industries needs to adopt ways to decrease the continuously high failure rate.<sup>[8]</sup> One of the most huge challenges in evaluating the success rate of clinical trials is entry of valid information on features of trial and their result.<sup>[9]</sup>

## 2. Reasons behind failure

- 1) Tuft's study- Centre for the Study of Drug Development(CSDD):** From 2000 to 2009, Evaluation of clinical found three basic common reasons of drug failure in phase3 trial are efficacy, safety, commercial/financial.<sup>[4]</sup> Among 344 unapproved agents 195 drugs failed due to lack of efficacy, 59 due to safety and 74 due to commercial/financial reasons and 16 were unable to identify the cause of failure.<sup>[9,10]</sup>
- 2) New Molecular Entities(NME) versus all drugs:** In every phase, the failure rate of NME trials were higher than all drugs trial were evaluated. In phase3 trials, only 61% of NME trials move further to next application phase(39% failure rate) whereas 67% of all drug trials move to the next phase(33% failure rate). High failure rate of NME trials are reported.<sup>[4]</sup>
- 3) Lack of commitment:** Lack of commitment is the primary reason for the high failure rate of drug as some companies only focus on their profit rather than focus on complete research process. The true commitment has not revealed by the industry about the immune system and

deep understanding of biology to flourish a blockbuster drug.<sup>[1]</sup>

- 4) **Dug failure in maternity:** Pharmaceutical companies are unwilling to test drugs in pregnant women because of extra price of toxicological reproductive studies.<sup>[12]</sup>
- 5) **Unable to meet regulatory requirements:** The most common cause of failure in clinical research is due to lack of ability to meet the requirements set by the FDA. Some companies can neglect the retaliation provided by FDA. Those companies that do not meet the regulatory necessities can deal with repudiation during later stages. So it is necessary to endow time and resources wisely and can assess all regulatory requirements alertly.<sup>[13]</sup>
- 6) **Inexperienced project manager:** Absence of risk management foresees and less inspiration of the team are notices as the most famous “fault” of a project manager. This will lead towards debilitated planning and execution of project failures.<sup>[14]</sup>
- 7) **Protocol Complexity:** The specialist stated that the more no. of protocol modification that must be follow, which may be lead to withdraw half of the initial endpoints, is a direct signal of protocol over complexity.<sup>[14]</sup>
- 8) **Inadequate confirmation and training:** One more reason discussed for failure is the absence of relevant training facilities of study sites. It is very likely discussed that the improper training will lead in ethical problems and poor quality data.<sup>[14]</sup>
- 9) **Ethical problems:** Ethical problems may lead to have a greater chances of trial failure , critically harm the status of all the parties which are involved like the CRO, the pharmaceutical physician and the pharmaceutical companies . There were many industries cases illustrate that so-called short term profit can promptly turn into long term harm.<sup>[14]</sup>
- 10) **Considering the patient’s financial burden:** The immense problem of clinical trials that fail due to the less recruitment, retention and enrollment, its prime value is in execute and designing of clinical trials regarded as the overburden that each patient undergoes with the faith that retention is associated negatively with patient should be attention, but financial impacts demands particular deliberation.<sup>[15]</sup> In many trials, demand for a subject to move to their particular study centers even for the the testing process which must be locally given or regulate at home. Patients required to migrate near to the study center for some period of time. The financial impact of some trials may destructively effect patient compliance as well as retention.<sup>[16,17,27]</sup>

### 3. Consequences after drug failure

1) **Impact on human:** Drug failure is one of the worst factor which impact human life badly. It leaves negative impact on humans **subjects** who participated in the clinical trial for better therapeutic outcome. As PARAXEL analysis conveys that in short time frame of 2012-2015, 150,000 subjects are participated in phase3 trials that failed ultimately. Many of the patients suffering from cardiovascular diseases, diabetes mellitus and cancer. In later disease stage having few standard treatment options by which the enrolling participants in clinical trial are often difficult to treat. For many of these patients, the one and only option for prevention or prolongation of life is clinical

trial.<sup>[4]</sup> However, the failed drug trial may have worsened impact on patient’s lifestyle, emotional health as well. About 75% of pregnant women are taking at least one drug for which the safety data is not available which may also leave negative impact on pregnant women and her unborn child. It will lead to lower success rate of drug or drug failure.<sup>[12]</sup>

2) **Financial impact:** Large pharmaceutical companies invest billions of dollars for invention of new drug. Majority of the drugs never make their standard in the market because during drug development stage majority of drugs show serious adverse event effects which will not used for therapeutic purpose. The cost of failed clinical trial is more so industries wants to adopt methods to reduce high failure rate. The high market price of drug affects industrial financial conditions.<sup>[1]</sup> Due to the high market price of drug some patients are not able to buy high priced medicines at affordable cost. So that it eventually leads to failure of drug.<sup>[1]</sup>

3) **Patent:** A successful invention is approved by regulatory authority such as FDA in US and EMA in Europe prior to be sold in market. The pharmaceutical companies already set the patent for the drug and are independent to sell the product in the market till the patent expiry. In developed countries like USA, Australia, UK, the time period for patent is granted for about 20 years and the company require patenting the drug prior to its first launch for the prevention of the intellectual property. During the short life span of patent, pharmaceutical industries has to recover all the expenses which were invested on R&D. Therefore patent life is one of the fundamental key sources of the income which can be produced from the product. The investors always try to extend the life of patent as much as possible. As the patent expires, the drug will be withdrawn from the market and it will lead to a many ups and down in the market share.<sup>[18]</sup>

4) **Sustaining a reasonable business:** The investors in pharmaceutical companies invest more money in the hope of getting more profit in return.<sup>[17]</sup> Company is a high risk based organization. Large and long lasting investment is the demand of industry, but has more chances of failure. The return on investment will be more when the important needs of pharmaceutical companies will be fulfilled. Although there must be a need of large number of patients who used the drugs formed in the company and also these patients are willing to pay for them by directly, via insurance or via taxation.<sup>[18]</sup> If investors are unable to fulfill the necessary needs of industry then it negatively affect the business due to which sustaining a viable business becomes more difficult and leads to drug failure.<sup>[18]</sup>

5) **Response of Placebo:** Drug failure is more common for disease with high placebo response example-Pain. According to FDA, there are two main reasons for phase3 failure and these are: The biomarker use in phase2 did not precisely estimate the phase3 outcome for oncology and the other reason is the mechanism of action of untested drugs. The main reason for the failure to reveal efficacy in phase3 is increased placebo response that includes number of treatment arms, time interval of clinical trials. Placebo

response is rapidly increasing over the year which is the main cause of drug failure.<sup>[8]</sup>

**6) Additional cost related with recruitment:** Beyond payment, the extra costs related with patient recruitment can be very tough to evaluate and highly variable, even within the same investigative area.<sup>[18,19]</sup> HCP must have a very notable impact on patient recruitment and retention. Retention can experience hardship when patients perceive support staff to be unconcerned or if they have to interface regularly within new staff members.<sup>[21]</sup> Uplifting of patient trust in the clinical trial process may be supposed to lead excellent patient participation.<sup>[22]</sup>

#### Ways to overcome the rate of failure

- 1) '5R' framework :** 5R framework is developed to upgrade the organization's health and to enhance the success rate of phase3 trials. The 5R framework directs R&D teams to identify *the Right target* with having strong link between target and disease and having anticipated biomarker, *the Right tissue* having drug-drug interaction and accurate understanding of preclinical and clinical PK/PD, *the Right safety* having understanding of target liability, *the Right patient* having identification of most susceptible patient population and *the Right commercial potential* that focus on market access.<sup>[4,5]</sup>
- 2) Early recognition of susceptible drug:** Due to inadequate efficacy, 50% of drugs fail in phase3 trial. Pharmaceutical companies spend more time on failure rather they need to save money by unhanding bad leads shortly. Identification of efficacy is done by biomarker testing and permits pharmaceutical companies to find susceptible drug candidates earlier and unhanding failed drug.<sup>[1]</sup> In order to ameliorate the drug development process, early analysis of new drug is essential.<sup>[23]</sup>
- 3) Anchorage large documentation:** Previously, the tremendous amount of data collected by the pharmaceutical companies is not precisely used. But now with advanced approaches and techniques the data is coordinated systematically to flourish new drug development plans and findings. Large documentation leads to more systematic and productive R&D and clinical process.<sup>[1]</sup>
- 4) Learn from failure:** Loss of money, resources and jobs are the results of failed clinical trials. The only comforting prospect of this failure is that it enables a change in the industry. The commercial pain of failure of the trial will ultimately motivate pharmaceutical companies and their shareholders to adopt innovative methods to reduce the chances of drug failure and which makes invention more systematic and successful.<sup>[1]</sup>
- 5) Conduct an Internal review:** By conducting an internal review of drug development processes that follows all the FDA guidelines leads to the success of the drug development process.<sup>[13]</sup>
- 6) Use of Innovative technologies:** Success rate of drug development process can be ameliorate by acquiring some innovative technologies like electronic health records, wearable's etc.<sup>[24]</sup> Some health mobile apps, social media also plays vital role in clinical progress by clarifying the issues of right patient enrollment and its maintenance and also helps in better

compliance.<sup>[25]</sup> Utilization of innovative technologies may make better compliance between the protocol as well as it can ameliorate safety of patient. Overall progress in technologies are remodeling the developers method to perform clinical trials and it could reform the future of trials.<sup>[26]</sup>

#### 4. Conclusion

Investigational drugs are failed in clinical trials due to inadequate efficacy and safety concerns. So pharmaceutical companies have to put more efforts to enhance drug development by adopting some innovative methods like 5R framework, early identification of susceptible drug promote companies to produce a blockbuster drug. The shareholders need to figure out the cause of failure in depth rather than to think about investment.

#### 5. Acknowledgement

I would like to thank Dr. Gurfatehsingh and Mr. Raibarindersingh for their thoughtful comments and suggestions that improved the quality of this review paper.

#### References

- [1] Huss R., 2016, "The High Price of Failed Clinical Trials: Time to Rethink the Model", Clinical Leader.
- [2] Hay M., Thomas W.D., Rosenthal J., Craighead J.L., Economides C., 2014, "Clinical development success rates for investigational drugs", Nature technology, 32, 40-51.
- [3] "Counting the cost of failure in drug development", 2017.
- [4] Grignolo A. and Pretorius S., 2016 "Phase III Trial Failures: Costly, But Preventable", Applied Clinical Trials.
- [5] Look D., Brown D., Alexander R., et al., 2014, "Lesson learned from the fate of Astrazeneca's drug pipeline: a five dimensional framework. Nat. Rev. Drug Discov., 13(6), 419-31
- [6] Williams R.J., Tse T., Depiazza K., Zarin D., 2015, "Terminated Trials in the clinical trials. Gov results database: evaluation of availability of primary outcome data and reasons for termination", PLoS One, 10.
- [7] Seruga B., Ocana A., Amir E., Tannock I.F., 2015, "Failures in Phase3: causes and consequences".
- [8] Schmith V., 2018, "Is Placebo Response Responsible for Many Phase 3 Failures?" NuventraPharma Sciences.
- [9] Wong C.H., Siah K.W., Andrew WLO., 2017 "Estimation of clinical trial success rates and related parameters", 20(2), 273-286.
- [10] Hwang T.J., Carpenter Daniel et.al., 2016, "Failure of Investigational Drugs in Late- Stage Clinical Development and Publication of Trial Results", JAMA Intern Med., 176(12).
- [11] Tufts CSDD, 2010-2011, "Comparative success rate for self originated, licensed in and small/large molecule drugs", A 2010 analysis PAREXEL's Bio/pharmaceutical R&D statistical sourcebook.

- [12] Fisk N.M., Atun R, 2008, "Market Failure and the Poverty of New Drugs in Maternal Health", *PLoS Med.*,5(1).
- [13] Plaford C., 2015, "Why do most clinical trials fail?", *Clinical Leader*.
- [14] Andrianov A., "Reasons why clinical trials fail?" Nipp R.D., Powell E., Chabner B., Moy B., 2015, "Recognizing the financial burden of cancer patients in clinical trials. *Oncology*", 20, 572-575.
- [15] Bernard D.S., Steptoe A., 2011, "National estimates of out of pocket healthcare expenditure burdens among nonelderly adults with cancer: 2001-2008", *Journal of clinical oncology*, 29, 2821-2826.
- [16] Covinsky K.E., Goldman L., Cook E.F., Oye R., Desbiens., Reding D., Fulkerson W., Connors A.F., Lynn J., Phillips R.S., 1994, "The impact of serious illness on patient families support investigators. Study to understand prognose and preferences for outcomes and risks of treatment", *Journal of American Med. Assoc.*, 272, 1839-1844.
- [17] Taylor D., 2015, "The Pharmaceutical Industry and the Future of Drug Development", *The Royal Society of Chemistry*.
- [18] Fogel D.V., 2018, "Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review", 156-164.
- [19] Okuyemik S., Cox L.S., Nollen N.C., Snow T.M., Kaur H., Chai W., Nazir N., Mayo M.S., Ahluwalia J.S., 2007, "Baseline characteristics and recruitment strategies in a randomized clinical trial of African-american light smoker", *American Journal of Health And Promotion*, 21, 186-191.
- [20] Dickson S.A., Logan J., Hagen S., Stark D., Glazener C., McDonald A.M., McPherson G., 2013, "Reflecting on the methodological challenges of recruiting to a united kingdom-wide, multicentre, randomized controlled trial in gynaecology outpatient settings trials", 14, 389.
- [21] Ward P.R., Rokkas p., Cenko C., Pulvirenti M., Dean N., Carney A.S., Meyer S., 2017, "Waiting for and waiting in public and private hospitals: a qualitative study of patient trust in south Australia, *MMC Health Serv. Res.*, 17, 333.
- [22] Mills R., 2016, "Why do drugs in development "Fail" in clinical trials?"
- [23] Parasrampur D.A., Benet L.Z., Sharma A., 2018, "Why drugs fail in Late stages of Development: case study analyses from the last decade and recommendations", *The AAAPS Journal* 20:46.
- [24] SRG, 2018, "What are the most promising clinical trial technologies?"
- [25] Lakeland j., 2017, "Technology Advancing clinical trials"
- [26] Zafar S.Y., Peppercorn J.M., Schrag D., Taylor D.H., Goetzinger A.M., Zhong X., Abernethy A.P., 2013, "The financial toxicity of cancer treatment. A pilot study assessing out of pocket expenses and the insured cancer patient's experience. *oncology*, 18, 381-390.